

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
17 July 2003 (17.07.2003)

PCT

(10) International Publication Number
WO 03/057179 A3

- (51) International Patent Classification⁷: **A61K 31/70**,
38/46, 39/395, C07K 1/00, C12P 21/06, 21/04, G01N
33/53
- (21) International Application Number: PCT/US03/00894
- (22) International Filing Date: 10 January 2003 (10.01.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/347,758 11 January 2002 (11.01.2002) US
- (71) Applicant (*for all designated States except US*):
BIOMARIN PHARMACEUTICAL, INC. [US/US];
371 Bel Marin Keys Blvd., Suite 210, Novato, CA 94949
(US).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): **STARR, Christo-
pher, M.** [US/US]; 19535 Seventh Street East, Sonoma,
CA 95476 (US). **ZANKEL, Todd** [US/US]; 46 Galli Drive,
Novato, CA 94949 (US).
- (74) Agent: **McMILLIAN, Nabeela, R.**; Marshall, Gerstein
and & Borun, 6300 Sears Tower, 233 South Wacker Drive,
Chicago, IL 60606-6402 (US).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE,
SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI,
SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN,
GQ, GW, ML, MR, NE, SN, TD, TG).
- Declaration under Rule 4.17:**
— *of inventorship (Rule 4.17(iv)) for US only*
- Published:**
— *with international search report*
- (88) Date of publication of the international search report:
4 December 2003
- For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: USE OF P97 AS AN ENZYME DELIVERY SYSTEM FOR THE DELIVERY OF THERAPEUTIC LYSOSOMAL ENZYMES

(57) Abstract: The present invention provides for compositions and methods for treating, ameliorating or preventing a lysosomal storage disease by administering to a patient suffering from a lysosomal storage disease a P97 conjugated with an enzyme which is capable of transportation into the lysosomes of cells on either sides of the blood brain barrier.

WO 03/057179 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/00894

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/70, 38/46, 39/395; C07K 1/00; C12P 21/06, 21/04; G01N 33/53
US CL : 424/94.6, 131; 435/7.1, 69.1, 69.7; 5124/25, 44; 530/350

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/94.6, 131; 435/7.1, 69.1, 69.7; 5124/25, 44; 530/350

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,866,042 A (NEUWELT) 12 September 1989 (12.09.1989), see Abstract, Table 1, Claim 6.	1-3, and 11-13
Y	US 5,672,683 A (FRIDEN et al.) 30 September 1997 (30.09.1997), see Column 1, Line 66 to Column 2, Line 52; Column 4, Line 50 to Column 5, Line 5; Column 5, Lines 19-34 and Column 41, Lines 18-25.	1-29
Y	US 5,981,194 A (JEFFRIES et al.) 09 November 1999 (09.11.1999), see Column 6, Lines 14-62; Column 8, Lines 54-67; Column 14, Line 51 to Column 15, Line 5; Column 29, Line 65 to Column 30, Line 35; Column 31, Lines 11 to 48; Column 39, Lines 9-57; Column 77, Lines 13-23 and Column 101, Line 1 to Column 102, Line 25.	1-29

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"B" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

24 July 2003 (24.07.2003)

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Facsimile No. (703)305-3230

Date of mailing of the international search report

Authorized officer

Dr. Kailash C. Srivastava

Telephone No. (703)-308-0196

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/00894

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US03/00894

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING:

Group I. Claims 1-13, 14-20 and 27-29

A method to treat a lysosomal storage disease in a subject by administering a pharmaceutical composition comprising a p97 protein conjugate (i.e., compound) and another method to screen for said compound.

Group I.1 Claims 1-13. A therapeutic method to treat a lysosomal storage disease.

1.2 Claims 14-20. A compound (i.e., p97 protein conjugate).

1.3 Claims 27-29 Application of said compound in a pharmaceutical composition.

Group II. Claims 21-26. A second method, i.e. an assay method to screen a compound for therapeutic activity to treat lysosomal storage disease, wherein compound comprises a p97 covalently linked to a protein.

The inventions listed as Groups I-II do not relate to a single special inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the scope of the product corresponding to the special technical feature is not coextensive for the two methods, i.e., two group of invention do not share a special technical feature.

Continuation of B. FIELDS SEARCHED Item 3:

JPAB, EPAB, PGPB, USPATFULL, BIOSIS, CONFSCI, IFIPAT, LIESCI, MEDLINE, SCISEARCH, WPIDS

Search Terms: conjugate near5 (p97 or MTf or melanotransferrin or melanoma associated antigen or p97-HRP, p97-horse radish peroxidase or p97-enzyme or p97-protein or cathepsin or fusion protein), lysosome replacement therapy, (lysosomal storage disease or LSDs or MPS I or MPS II or MPS III or GM I or Gaucher or (lysosomal enzyme dysfunction)), (p97 and beta glycosidase) or (p97 and alpha-L-iduronidase), (metachromatic leuko dystrophy or Alzheimer's disease) or (lysosomal enzyme dysfunction), blood brain barrier or BBB.